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EXAMINER
HUYNH, PHUONG N

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/006,163	Applicant(s) LAL ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11,30-45,56 and 58* is/are pending in the application.

4a) Of the above claim(s) *1,30,33,35,44,45 and 56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11, 31-32, 34, 36-43 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1, 11, 30-45, 56 and 58 are pending.

2. Applicant's election with traverse of Group II, Claims 11, 31-32, 34 and 36-43 (now claims 11, 31-32, 34, 36-43 and 58) drawn to antibodies which specifically bind to polypeptide of SEQ ID NO: 1, compositions comprising said antibodies and a method of making antibodies, filed 6/3/02, is acknowledged. The traversal is on the grounds that the claims directed to various methods of using the claimed antibodies (1) for diagnosing a condition or disease (claims 30, 33 and 35), (2) for detecting a polypeptide of SEQ ID NO: 1 (Claim 44) and (3) for purifying polypeptide of SEQ ID NO: 1 (claim 45) should be examined together without undue burden on the Examiner. This is not found persuasive because of the reasons set forth in the restriction mailed 5/7/02. The inventions are distinct, each from the other because of the following reasons:

Inventions of Groups I-III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the polypeptide, antibody and polynucleotide differ with respect to their structure and physiochemical properties. Therefore, they are patentably distinct.

Inventions of Groups IV-VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the methods of diagnosing a condition in vitro versus in vivo, and the method of purifying a polypeptide differ with respect to their process steps and endpoints. Therefore, they are patentably distinct. Inventions of Group II and Groups (IV-V) are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the antibody as claimed can be used in materially different process such as treating an immune disorder. Therefore, they are patentably distinct. Further, Groups I-V differ with respect to their Class and subclass. A prior art search of Group II will not encompass Groups IV-VI. It is a burden to search more than one

invention. Therefore, the requirement of Group II (now claims 11, 31-32, 34, 36-43 and 58) and Groups I and III-VI is still deemed proper and is therefore made FINAL.

3. Claims 1, 30, 33, 35, 44-45 and 56 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 11, 31-32, 34, 36-43 and 58 are being acted upon in this Office Action.

5. The references on PTO 1449, filed 12/4/01 have been crossed out because none of the references have been submitted to the Office.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 11, 31-32, 34, 36-43 and 58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, (2) a composition comprising said antibody and an acceptable excipient for competitive binding or immunoradiometric assays or for detection assays, (3) the said composition wherein the antibody is labeled, (4) a method of preparing polyclonal, or monoclonal antibody with the specificity of the antibody that binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, (5) a polyclonal or a monoclonal antibody produced by said method, (6) a composition comprising said polyclonal or monoclonal antibody, and a suitable carrier, and (7) the said antibody wherein the antibody is produced by screening a Fab expression library, or recombinant immunoglobulin library, **does not** reasonably provide enablement for (1) *any* isolated antibody which specifically binds to (a) *any* polypeptide comprising *any* naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 wherein said polypeptide has CoA dehydrogenase activity, (b) *any* fragment of a polypeptide "having" the amino acid sequence of SEQ ID NO: 1, (c) *any* fragment "comprises at least *any* 15 contiguous amino acid sequence residues of SEQ ID NO: 1, (2) any antibody which specifically binds to (a) *any* polypeptide comprising *any* naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:

1 wherein said polypeptide has CoA dehydrogenase activity, (b) *any* fragment of a polypeptide "having" the amino acid sequence of SEQ ID NO: 1, (c) *any* fragment "comprises at least *any* 15 contiguous amino acid sequence residues of SEQ ID NO: 1 wherein the antibody is (a) a chimeric antibody, (b) a single chain antibody, (c) a Fab fragment, (d) a F(ab')2 fragment or (e) a humanized antibody, (3) *any* composition comprising *any* antibody mentioned above and an acceptable excipient, (4) *any* composition comprising *any* antibody mentioned above and an acceptable excipient wherein the antibody is labeled, (5) a method of preparing *any* polyclonal or monoclonal antibody with the specificity of *any* isolated antibody which specifically binds to (a) *any* polypeptide comprising *any* naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 wherein said polypeptide has CoA dehydrogenase activity, (b) *any* fragment of a polypeptide "having" the amino acid sequence of SEQ ID NO: 1, (c) *any* fragment "comprises at least *any* 15 contiguous amino acid sequence residues of SEQ ID NO: 1, (6) *any* polyclonal or monoclonal antibody produced by immunizing an animal with *any* polypeptide comprising *any* naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 wherein said polypeptide has CoA dehydrogenase activity, (b) *any* fragment of a polypeptide "having" the amino acid sequence of SEQ ID NO: 1, (c) *any* fragment "comprises at least *any* 15 contiguous amino acid sequence residues of SEQ ID NO: 1, (7) *any* composition comprising *any* polyclonal or *any* monoclonal antibody mentioned above and a suitable carrier, (8) any antibody mentioned above wherein the antibody is produced by screening a Fab expression library, or a recombinant immunoglobulin library, (9) *any* isolated antibody which specifically binds to *any* immunogenic fragment of a polypeptide consisting of the amino acid sequence of SEQ ID NO: 1 wherein said fragment "comprises" at least 15 contiguous amino acid residues of SEQ ID NO: 1 for treating any immune disorder and cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient

to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only antibody that specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, a composition comprising said antibody for diagnostic and detection assays. The specification on page 14 discloses a "variant" of human short chain dehydrogenase (HSCD) is any amino acid sequence that is altered by one or more amino acids such as substitution, insertion and deletion (See page 14 of specification, second full paragraph).

The specification does not teach how to make and use *any* antibody mentioned above for treating any immune disorder and cancer because there is insufficient guidance as to which undisclosed antibody would binds to *any* naturally occurring amino acid sequence at least 90% identical (at least 10% difference) to the amino acid sequence of SEQ ID NO: 1 with the same specificity as the antibody that binds to the full length polypeptide comprising SEQ ID NO: 1. A ten percent difference of SEQ ID NO: 1 is equivalent to 31 amino acids difference and the is insufficient guidance as to the specific amino acid residues (antigenic determinant) within polypeptide of SEQ ID NO: 1 can be change such as substitution, deletion, and insertion, in turn, the claimed antibody would still binds specifically to a polypeptide comprising *any* naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 with the same specificity as the antibody that binds to the full length polypeptide comprising SEQ ID NO: 1. Further, there is insufficient guidance as which undisclosed antibody (antibody binding specificity) would specifically binds to *any* fragment "comprises at least *any* 15 contiguous amino acid sequence residues of SEQ ID NO: 1, *any* fragment "comprises *any* 15 contiguous amino acid sequence residues of SEQ ID NO: 1. The term "having" or "comprising" is open-ended. It expands the polypeptide fragment to which the antibody binds to include additional amino acid residues at either or both ends, in turn, would be useful for any purpose.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Kuby *et al* teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues (fragment) or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-

length polypeptide, let alone a polypeptide with 10% difference. Without the specific amino acid residues (the antigenic determinant), it is unpredictable to determine which undisclosed antibody response generated from an indefinite number of undisclosed polypeptide having addition, deletion, and insertion will have the same antibody specificity as an antibody generated from the full length polypeptide of SEQ ID NO: 1, in turn, would be useful even for any binding assays. Since the specification fails to provide guidance with regard to the antigenic determinant (peptide) of any undisclosed antibody, it follows that the method of making *any* monoclonal antibody, polyclonal antibody, chimeric, single chain, humanized antibody, Fab fragment, F(ab')2 fragment, and composition comprising said antibody mentioned above produced by screening a Fab expression, screening a recombinant immunoglobulin library are not enable. It also follows that any composition comprising any antibody mentioned above is not enable.

With regard to composition comprising any polyclonal or monoclonal antibody with the specificity mentioned above and an acceptable excipient or suitable carrier, the specification fails to provide any *in vivo* working examples, or guidance with respect to treating a patient suffering from *any* specific disease using *any* antibody mentioned above.

The '370 patent teaches that the inherent problem with chimeric antibody has been a loss of affinity for the antigen, which means more antibody will have to be injected into a patient at higher cost and greater risk of adverse effects such as serum sickness (See column 2 lines 12-27, in particular). In the absence of in vivo working examples, it is unpredictable for the following reasons: (1) the antibody may be inactivated before producing an effect, i.e. such as inherently short half-life of the antibody; (2) the antibody may not reach the target area; and (3) other functional properties, known or unknown, may make the antibody unsuitable for *in vivo* therapeutic use, i.e. such as serum sickness which prohibitive to the use of antibody for such treatment. Therefore, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. Claims 11, 31-32, 34, 36-43 and 58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* isolated antibody which specifically binds to (a) *any* polypeptide comprising *any* naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 wherein said polypeptide has CoA dehydrogenase activity, (b) *any* fragment of a polypeptide "having" the amino acid sequence of SEQ ID NO: 1, (c) *any* fragment "comprises at least *any* 15 contiguous amino acid sequence residues of SEQ ID NO: 1, (2) any antibody which specifically binds to (a) *any* polypeptide comprising *any* naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 wherein said polypeptide has CoA dehydrogenase activity, (b) *any* fragment of a polypeptide "having" the amino acid sequence of SEQ ID NO: 1, (c) *any* fragment "comprises at least *any* 15 contiguous amino acid sequence residues of SEQ ID NO: 1 wherein the antibody is (a) a chimeric antibody, (b) a single chain antibody, (c) a Fab fragment, (d) a F(ab')2 fragment or (e) a humanized antibody, (3) *any* composition comprising *any* antibody mentioned above and an acceptable excipient, (4) *any* composition comprising *any* antibody mentioned above and an acceptable excipient wherein the antibody is labeled, (5) a method of preparing *any* polyclonal or monoclonal antibody with the specificity of *any* isolated antibody which specifically binds to (a) *any* polypeptide comprising *any* naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 wherein said polypeptide has CoA dehydrogenase activity, (b) *any* fragment of a polypeptide "having" the amino acid sequence of SEQ ID NO: 1, (c) *any* fragment "comprises at least *any* 15 contiguous amino acid sequence residues of SEQ ID NO: 1, (6) *any* polyclonal or monoclonal antibody produced by immunizing an animal with *any* polypeptide comprising *any* naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 wherein said polypeptide has CoA dehydrogenase activity, (b) *any* fragment of a polypeptide "having" the amino acid sequence of SEQ ID NO: 1, (c) *any* fragment "comprises at least *any* 15 contiguous amino acid sequence residues of SEQ ID NO: 1, (7) *any* composition comprising *any* polyclonal or *any* monoclonal antibody mentioned above and a suitable carrier, (8) any antibody mentioned above wherein the antibody is produced by screening a Fab expression library, or a recombinant immunoglobulin library, (9) *any* isolated antibody which specifically binds to *any* immunogenic

fragment of a polypeptide consisting of the amino acid sequence of SEQ ID NO: 1 wherein said fragment "comprises" at least 15 contiguous amino acid residues of SEQ ID NO: 1 for treating any immune disorder and cancer.

The specification discloses only antibody that specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, a composition comprising said antibody for diagnostic and detection assays. The specification on page 14 discloses a "variant" of human short chain dehydrogenase (HSCD) is any amino acid sequence that is altered by one or more amino acids such as substitution, insertion and deletion (See page 14 of specification, second full paragraph).

With the exception of the specific antibody that binds to the specific polypeptide mentioned above, there is insufficient written description about the structure associated with function of any isolated antibody which specifically binds to (1) *any* polypeptide comprising *any* naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 wherein said polypeptide has CoA dehydrogenase activity, (2) *any* fragment of a polypeptide "having" the amino acid sequence of SEQ ID NO: 1, (3) *any* fragment "comprises" at least *any* 15 contiguous amino acid sequence residues of SEQ ID NO: 1 for treating, diagnosing and detecting polypeptide of SEQ ID NO: 1. A ten percent difference of SEQ ID NO: 1 is equivalent to 31 amino acids difference and there is insufficient written description about the specific amino acid residues (antigenic determinant) within polypeptide of SEQ ID NO: 1 can be change such as substitution, deletion, and insertion. Further, the term "having" or "comprising" is open-ended. It expands the polypeptide fragment to include additional amino acid residues at either or both ends to which the antibody binds. There is inadequate written description about which 15 contiguous amino acid of SEQ ID NO: 1 is useful for making antibody that would have the same binding specificity as the full length polypeptide of SEQ ID NO: 1. Finally, given the lack of a written description of any additional antibody that binds to SEQ ID NO: 1, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 11 and 36-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Verwoert *et al* (J Bioteriol 174: 2851-57, 1992; PTO 892).

Verwoert *et al* teach an antibody that binds to a fragment such as VTGASRGIGRGIA of a polypeptide such as Malonyl coenzyme A-Acyl carrier protein transacylase that has a stretch of contiguous amino acid residues identical to the claimed SEQ ID NO: 1 (See Fig 2, last full line, Fig 3, page 2853, in particular). Verwoert *et al* teach a method of preparing a polyclonal antibody comprising immunizing an animal such as a mouse with the reference polypeptide (See Production of Antibodies and Immunodetection, in particular). While the reference is silent that the reference polypeptide fragment has the functional properties of has CoA dehydrogenase activity, the reference antibody has the specificity of the claimed antibody and the functional properties would be an inherent property of the polypeptide to which the antibody binds. Therefore the claimed antibody appears to be the same as the prior art antibody. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Thus, the reference teachings anticipate the claimed invention.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 11, 31, 42 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Verwoert *et al* (J Bioteriol 174: 2851-57, 1992; PTO 892) in view of US Pat No. 6,180,370B, filed June 1995; PTO 892).

The teachings of Verwoert *et al* have been discussed supra. Verwoert *et al* further teach the reference polypeptide is a temperature labile malony CoA ACP transacylase that plays a role in transferring the malonyl and/or acetyl group in the biosynthesis of polyketides (See page 2855, Discussion, in particular) Verwoert *et al* teach the reference antibody is useful for immunodetection (See page 2853, column 1, in particular).

The claimed invention in claim 31 differs from the reference only by the recitation that the antibody is a chimeric antibody, or a humanized antibody.

The claimed invention in claim 42 differs from the reference only by the recitation that screening a Fab expression library produces the antibody.

The claimed invention in claim 43 differs from the reference only by the recitation that screening a recombinant immunoglobulin library produces the antibody.

The '370 patent teaches a method of producing chimeric antibodies (See column 55 lines 25-59; column 59, lines 65; in particular) and humanized antibodies (See column 44 line 33; column 68 lines 8-44, in particular) by screening a Fab expression library or a recombinant immunoglobulin library. The reference chimeric antibody comprises a variable region of an antibody and a human immunoglobulin constant region. The '370 patent further teaches that the chimeric humanized immunoglobulins (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce chimeric antibody or humanized antibody as taught by the '370 patent that binds specifically to the polypeptide fragment as taught by Verwoert *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.
One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '370 patent teaches that the chimeric humanized immunoglobulins (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular). Verwoert *et al* teach the reference antibody to the reference polypeptide is useful for immunodetection (See page 2853, column 1, Discussion, in particular).

14. Claims 11 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Verwoert *et al* (J Bioteriol 174: 2851-57, 1992; PTO 892) in view of US Pat No. 4,946,778 (Aug 1990, PTO 892).

The teachings of Verwoert *et al* have been discussed supra.

The claimed invention in claim 31 differs from the reference only by the recitation that the antibody is a single chain antibody.

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody or a polypeptide fragment (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to make single chain antibody as taught by the '778 patent that binds specifically to the polypeptide fragment as taught by the Verwoert *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '778 patent teaches the advantages of a single chain antibody are

small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

15. Claims 11, 31-32, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Verwoert *et al* (J Bioteriol 174: 2851-57, 1992; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 319-356, and 626-629).

The teachings of Verwoert *et al* have been discussed supra.

The claimed invention as recited in claim 31differs from the reference only by the recitation that the antibody is a Fab fragment, a F(ab')2 fragment.

The claimed invention as recited in claim 32 differs from the reference only by the recitation of a composition comprising said antibody and an acceptable excipient.

The claimed invention as recited in claim 34 differs from the reference only by the recitation the antibody is labeled.

Harlow *et al* teach a method of producing antibody fragment wherein the fragment is Fab or F(ab')2 fragment (See page 626-629, in particular). Harlow *et al* teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular). Harlow *et al* further teach labeling any antibody with various labels such as enzyme or FITC (See chapter 9, in particular) in a composition comprising an antibody and a carrier such as PBS (See page 354, in particular) or NaCl, which is a saline solution (See page 346, in particular) for various detection assays. The advantages of enzyme labeling are longer shelf life, and higher sensitivity while the advantages of fluorochrome label are long shelf life and good resolution in immunohistochemistry (See page 322, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce antibody fragment such as Fab or F(ab')2 or to label any antibody as taught by Harlow *et al* with the polyclonal antibody that binds specific to a fragment comprises a contiguous amino acid residues of the claimed SEQ ID NO: 1 as taught by Verwoert *et al* or Harlow *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach antibody fragments can overcome the problem of capping and internalization of the antigen on mammalian cell when using multivalent antibodies (See page 626 in particular) and the labeled antibody can be used for various detection assays. The advantages of enzyme labeling are longer shelf life, higher sensitivity while the advantages of fluorochrome label are long shelf life and good resolution in immunohistochemistry (See page 322, in particular).

16. Claims 11 and 38-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Verwoert *et al* (J Bioteriol 174: 2851-57, 1992; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 139-149).

The teachings of Verwoert *et al* have been discussed supra.

The claimed invention as recited in claim 38 differs from the reference only by the recitation a composition comprising the polyclonal antibody and a suitable carrier.

The claimed invention as recited in claim 39 differs from the reference only by the recitation a method of making monoclonal antibody comprising immunizing an immunogenic fragment thereof.

The claimed invention as recited in claim 40 differs from the reference only by the recitation that a composition comprising the monoclonal antibody produced by the method of claim 39.

The claimed invention as recited in claim 41 differs from the reference only by the recitation a composition comprising the monoclonal antibody and a suitable carrier.

Harlow *et al* teach a method of producing polyclonal antibody using rabbit for practical reasons because they are easy to keep and handle and antibody produced are well characterized and easily purified (See page 93, in particular). Harlow *et al* further teach a method of producing monoclonal antibody (See page 139-149, in particular) and the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full paragraph, in particular). Harlow *et al* further teach labeling any antibody with various label such as enzyme or FITC (See chapter 9, in particular) in a composition comprising an antibody and a carrier such as PBS (See page 354 in particular) or NaCl, which is a saline solution (See page 346) for various detection assays. The advantages of enzyme labeling are longer shelf life, higher sensitivity while the advantages of fluorochrome

label are long shelf life and good resolution in immunohistochemistry (See page 322, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce monoclonal antibody as taught by Harlow *et al* with the polypeptide as taught by Verwoert *et al* for a composition comprising said antibody and a carrier such as PBS as taught by Harlow *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to make antibody fragment because Harlow *et al* teach that the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full paragraph, in particular).

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

19. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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